The Status of the Claims.

Claims 22-46 are pending with entry of this amendment, with claims 31-43 being withdrawn from current consideration. Claim 21 is amended herein and Claims 44 through 46 are newly added. These amendments introduce no new matter and support is replete throughout the specification. The amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

Applicants submit that no new matter has been added to the application by way of the above amendments. Accordingly, entry of the amendments is respectfully requested.

Objections to the Claims.

Claim 22 was objected to in the Office Action due to a typographical error (i.e., 'tumor' was misspelled as 'tumore'). Applicants amend Claim 22 herein and respectfully request that the objection be withdrawn.

35 U.S.C. §112, First Paragraph.

Claims 22-27 and 30

Claims 22-27 and 30 were rejected in the Office Action under 35 U.S.C. §112, first paragraph for containing subject matter not described in the specification so as to reasonably convey that the inventors had possession of the claimed invention. More specifically, the Office Action alleges that the specification does not have adequate structural description of the genus of compounds encompassed by the claim phrases: an "inositolphosphoglycan antagonist," a "substance which is capable of inhibiting the release of IPGs," a "substance capable of reducing the levels of IPGs by binding to the IPGs," a "substance which is a competitive agent which is capable of reducing an effect of IPGs," "a competitive IPG antagonist," an "antibody [...] capable of neutralizing an activity of IPGs," and an "inhibitor of glycosylphosphatidylinositol specific phospholipase type C."

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See*, Vas-Cath, Inc. v. Mahurkar, 935 F.2d (1991) at 1563.

The Office Action purports that the specification only describes three IPG antagonists (three monoclonal antibodies) which are not representative of the genus of compounds encompassed by the various functional limitations of the claims. More specifically, the Office Action describes the antibodies as being IPG antagonists, but alleges that the specification does not have any example of their neutralization of any IPG activity and that the antibodies do not demonstrate any of the activities of the broad classes of IPG inhibitors recited in the claims (e.g., that the antibodies inhibit release of IPGs, that the antibodies are competitive agents with IPGs or that the antibodies inhibit glycosylphosphatidylinositol specific phospholipase type C). Applicants respectfully traverse.

The claims recite use of IPG antagonists having the property of reducing tumor cell proliferation. Applicants have shown for the first time that IPGs can act as tumor autocrine factors, and so have claimed methods of reducing tumor proliferation that rely on this technical teaching and that correspond to such contributions provided by the invention. In the claims, these antagonists are subdivided into three different categories (i) agents capable of inhibiting release of IPGs, *see*, Claim 24a, (ii) agents capable of reducing the levels of IPGs by binding to them, *see*, Claim 24b, and (iii) agents which are competitive inhibitors of IPG activity, *see* Claim 24c.

Applicants respectfully point out that the monoclonal antibodies described in the specification are examples of the second category (i.e., agents capable of reducing the levels of IPGs by binding to them). This is clear from claim 26 and from the description as a whole (*see*, e.g., page 3, lines 10 to 15 and page 5, lines 8-14, etc.). It is also clear from the description that these antibodies are capable of neutralizing the tumor cell proliferation caused by IPGs, *see*, description spanning pages 24 and 25, and Figure 4, which show inhibition of FaO cell proliferation by the three named monoclonal antibodies.

Thus, it is incorrect to assert that the specification does not show "any examples of antibodies capable of neutralizing an activity of IPGs" or that "[t]he antibodies described in the specification are not demonstrated to have any of the activities of the broad classes of IPG inhibitors that are recited in the claims." The specification clearly illustrates antibodies capable of neutralizing an IPG activity and having an activity of an IPG inhibitor as recited in the claims.

In regard to the recited antibodies inhibiting the release of IPGs or competitively binding, it is correct that the named antibodies do not have the other two properties recited in the claims (i.e., the claims do not recite antibodies which inhibit release of IPGs or competitively inhibit IPG activity). However, the specification provides specific examples and ample guidance for a skilled person to produce both of these other types of IPG antagonists. For example, inhibitors of GPI-specific phospholipases may be used to inhibit release (*see*, page 2, lines 30-33; page 3, lines 17-22). Those of skill in the art will be familiar with various possible inhibitors of such enzymes. Also, as in Claim 24c, IPGs from other species, which are biologically inactive in the species to which they are to be administered, may be used as competitive inhibitors of IPG activity. For example, porcine liver A-type IPG may be used to inhibit human IPG activity. *See*, e.g., page 12, line 32 through page 13, line 18. Methods of preparing IPGs are also described at page 7, line 15 through page 8, line 7.

Thus, the 3 classes of IPG antagonists (e.g., as in Claims 22 and 24) which are described by the claim phrases above, are supported and described in the specification and claims. Thus, the claims presented are, indeed, supported in the specification so that one skilled in the art would appreciate that the inventors were in possession of the claimed invention at the time of filing. Because of the above points, Applicants respectfully request that the rejection be withdrawn.

Claim 29

Claim 29 was rejected in the Office Action as containing subject matter not set forth so as to enable one skilled in the art to make and/or use the invention. Namely, the full address of the culture depository to which the antibody producing hybridomas were deposited was not given. As per the Examiner's suggestion, Applicants herein amend the specification to list the full address of the culture depository. Additionally, Applicants herewith submit copies of the deposit receipts for the hybridomas. Because the full address of the depository is now given, Applicants respectfully request that the rejection be withdrawn.

35 U.S.C. §102.

Claims 22-25 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by Levitzki et al. (U.S. Patent 5,932,580, filed December 1, 1997 and issued August 3, 1999) as evidenced by Nazih-Sanderson et al. (Biochemica et Biophysica Acta 1346:45-60, 1997).

In order for a reference to anticipate an invention, the reference must teach each and every element of the claimed invention. Anticipation requires that "all limitations of the claim are found in the reference, or 'fully met' by it." Kalman v. Kimberly-Clark Corp., 218 USPQ 781, 789 (Fed. Cir. 1983).

The examiner bases the current rejection on the assertion that "IPG is a mitogenic signaling mediator that is generated upon proteolytic cleavage of GPI-anchored proteins." This is derived from Nazih-Sanderson et al. at page 46, top of second column.

However, as explained by Varela-Nieto et al. (Comp. Biochem. Physiol. 115B(2):223-241), Nazih-Sanderson's assertion is incorrect. In particular, the first paragraph of the section headed "IPG generation from GPI precursors," (*see*, page 227, column 2 of Varela-Nieto) explains that there is uncertainty about whether IPG signaling mediators are derived from GPI membrane anchors or from free GPI. Varela-Nieto states that, on balance, the evidence demonstrates that the different functions described for GPI molecules are achieved by distinct members of the GPI family. Thus, free GPI and GPI anchors are different chemical species. Free GPI is the source of the IPG signaling mediators and these free GPIs are not derived from proteolytic cleavage of GPI anchors. In particular there is evidence that free GPI and GPI anchors have different chemical compositions, radiolabelling of rat liver plasma membrane lipids shows that free GPI is not derived from proteolysis of GPI anchors, and mutant T cell clones with impaired GPI-protein linkage synthesis are still able to produce insulin sensitive GPI at the cell surface. Varela-Nieto et al. state that "[i]t seems likely, therefore, that free-GPI is the physiological precursor of the IPG second messenger."

The inhibitor of tyrosine kinases described in Levitzki acts to prevent cleavage of GPI anchors. However, because such GPI anchors are not the source of IPG signaling mediators as involved in the current claims (*see*, above) tyrosine kinase inhibitors do not prevent release of such IPG mediators.

Therefore, because they do not involve IPG antagonists (because they concern blocking cleavage of GPI anchors not free GPI, which is the source of IPG signaling mediators), neither Nazih-Sanderson nor Levitzki, either alone or in combination, supplies all of the required limitations of the present claims. Applicants respectfully request that the rejection be withdrawn.

35 U.S.C. §103(a).

Claims 22-28 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Varela-Nieto et al, Comp. Biochem. Physiol., 115B(2):223-241, 1996 in view of Rademacher (WO98/11116, published March 19, 1998).

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference(s) must teach all of the limitations of the claims. M.P.E.P § 2143.03. Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention. M.P.E.P. § 2143.01. Third, a reasonable expectation of success is required. M.P.E.P. § 2143.02. Furthermore, the teaching or suggestion to combine, and the expectation of success, must both be found in the prior art references and not be based on the Applicants' disclosure. M.P.E.P. §2143.

The main passage cited for support of the obviousness rejection (Varela-Nieto et al., page 229, col. 2) states that anti-IPG antibodies inhibit growth factor-stimulated proliferation of

cochleovestibular ganglion (CVG) cells. However Varela-Nieto et al. are mistaken in their description of this work.

As described above, Varela-Nieto et al. view that IPG signaling mediators are not derived from GPI anchors, but rather from free GPI. However, the antibodies used to inhibit proliferation of CVG cells are polyclonal antibodies raised against the GPI anchor moiety of the VSG protein from trypanosome parasites. Varela-Nieto's generation and characterization is described by Romero et al. *See*, Romero et al., PNAS, USA, 87:1476-1480 (1990) a courtesy copy of which is enclosed herewith. There is no evidence that these polyclonal antibodies function as anti-IPG antibodies (i.e., as antagonists as used in the current claims, *see*, above), nor is their mechanism of action against CVG cells known.

Those skilled in the art would read Varela-Nieto's statements in conjunction with one another (*see*, above) and, thus, realize the inconsistencies in their position on the likely source of IPG mediators. Thus, Varela-Nieto should not be read as showing that antibodies directed against IPGs can block cellular proliferation.

Furthermore, although Varela-Nieto implicate IPGs in various second messenger systems (*see*, pages 232 to 233), this is quite a stretch from teaching that blockade of IPGs can inhibit those systems. No evidence to that effect is presented other than that relating to anti-GPI anchor antibodies already described, which, it will be appreciated, relate to normal cells and not tumor cells.

Thus, Varela-Nieto, even when read with Rademacher, do not have all of the elements of the current claims (e.g., they do not have an IPG antagonist as used in the present claims since their antibodies were raised against GPI anchors, etc.). Also, because of the inconsistencies in Varela-Nieto, there is no motivation for a skilled person to try to block tumor cell proliferation by use of anti-IPG antibodies (e.g., from Rademacher) as used in the recited claims. Even if a skilled person were to try to do so, no realistic expectation of success could be based on the evidence available. Thus, the combined cited references do not meet the criteria required for an obviousness rejection – all the elements of the required claims are not present, there is no motivation to combine present in the references, no expectation of success exists for their combination, etc. Applicants therefore respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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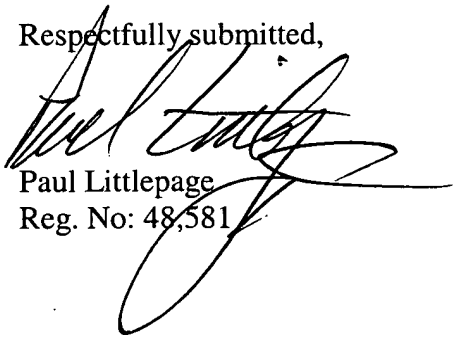
Respectfully submitted,



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